Remarks/Arguments

The foregoing amendments to the claims are of a formal nature and do not add new matter. Applicants thank the Examiner for considering the IDS filed 31 May 2002 in the current application. Claims 119-138 are pending herewith and are rejected on various grounds. Merely to expedite prosecution in this case, all pending claims have been amended to remove references to "Figures," to the "extracellular domain" and to references to polypeptides that are encoded by nucleic acids. Further, claims 119-123 have been amended with the functional recitation "wherein, said nucleic acid is amplified in lung tumors," support for which is found in the instant specification, at least in Example 170. Claims 125-128 and 132-134 have been canceled without prejudice of disclaimer. Accordingly, Claims 119-124, 129-131, 135-138 are currently pending in this application; rejections to these claims are respectfully traversed.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-138 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 119-138 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

The Examiner points out that "function cannot be predicted based solely on structural similarity to a protein found in the sequence databases" and quotes exemplary literature reports like Karp and Skolnick *et al.* to support this position. The Examiner further asserts that "the instant specification does not provide utility for nucleic acids encoding the polypeptide because the increased copy number of DNA does not provide a readily apparent use for the polypeptide". While the Examiner acknowledges that the nucleic acids encoding PRO1187 shows a positive correlation for lung cancer, the Examiner quotes Haynes *et al.*, Pennica *et al.* and Konopka *et al.* to show that "protein expression shows a poor correlation with mRNA expression" and further says that "the increased copy number of DNA does not provide a readily apparent use for the polypeptide, for which there is no information regarding level of expression, activity or role in

cancer". Regarding the gene amplification assay, the Examiner further asserted that "the specification does not provide a substantial utility for isolated nucleic acids" since the specification "fails to disclose the significance of the deltaCt values". The Examiner also quotes an exemplary reference by Sen to support that she is "unable to find in the specification that the deltaCt data was corrected for aneuploidy" and asserts that "a slight amplification of a gene does not necessarily mean that the gene is overexpressed in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid, which is commonly observed in human tumors". For the reasons outlined below, Applicants respectfully disagree.

Utility Guidelines

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that **Office personnel must be careful not to interpret the phrase "immediate benefit to the public"** or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the

assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Arguments

Initially, Applicants submit that the claimed utility for the PRO1187 nucleic acids is based on its use in the diagnosis of lung cancer and is not based on structural similarity to known proteins. As explained below, Applicants rely on the gene amplification data for patentable utility of this case. Further, without acquiescing to the propriety of the Examiner's rejection directed to PRO1187 polypeptides for lack of utility, Applicants have canceled claim subsets a, b, c and d which refer to nucleic acids encoding polypeptides, merely to expedite prosecution in this case. Hence, the rejections citing Haynes, Konopka and Pennica are moot, since the pending claims now refer to nucleic acids defined by SEQ ID NO: 398 alone.

Gene amplification is an essential mechanism for oncogene activation and the assay is well-described in Example 170, page 539 of the present application. The gene amplification data shows that genomic DNA was isolated from a variety of primary cancers and cancer cell lines listed in Table 9 (especially page 554, Table 9C) which includes primary lung cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the

cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29). Gene amplification was monitored using real-time quantitative TaqMan™ PCR and the results are set forth in Table 9C. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Applicants further submit a declaration by Dr. Audrey Goddard, a co-inventor of this application and an expert in the "gene amplification assay" who says in the declaration that a 2-fold amplification is considered significant. Table 9C indicates that PRO1187 showed approximately 1.17-1.55 ΔCt units which corresponds to $2^{1.17}$ -2 $^{1.55}$- fold amplification or **2.25- fold to 2.928-fold** amplification in squamous cell carcinomas of lung (see Table 8, page 546), which is significant and thus the PRO1187 gene has utility as a diagnostic marker for lung cancer.

Further, regarding the Examiner's rejection that there is a lack of correction of gene amplification data based on aneuploidy, Applicants submit that, as rightly noted by the Examiner and the Sen article, aneuploid tissues are **cancerous or pre-cancerous**. The present invention is directed to nucleic acids useful in the detection of cancer, irrespective of the mechanism by which gene amplification occurs. Even if the presence aneuploid cells or tissues were to predict a propensity towards cancer, the instant nucleic acids are still useful as diagnostic tools. Applicants have further included a declaration by Avi Ashkenazi, Ph.D., a co-inventor of this application, who says that:

> "An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes."

Therefore, a person of skill in the art would certainly consider the gene amplification results as significant and diagnostic for lung tumors. Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1187 nucleic acid based on the gene

amplification results. Further, one skilled in the art, at the time the application was filed, would know how to use the claimed nucleic acids, without undue experimentation.

Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

Claim Rejections – 35 USC § 112, first paragraph- Written description

Claims 119-123, 132-138 are rejected under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. The Examiner contends that the claims contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection to the pending claims.

The Legal standard for Written Description

The well- established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *In re* Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F. 2d at 1563, 19 USPQ2d at 1116 (Fed. cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. see e.g.Vas-Cath, Inc. v. Mahurkar, 935 F. 2d at 1563, 19 USPQ2d at 1116 (Fed. cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F. 3d 989, 996 (Fed. Cir. 2000).

Arguments

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of

his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

Without acquiescing to the propriety of this rejection, Applicants have amended the pending claims to recite a functional recitation: "wherein the nucleic acid encoding said polypeptide is amplified in lung tumors" and to refer to nucleic acids of SEQ ID NO: 398 alone. Further, the Written Description Guidelines issued by the U.S. Patent Office clearly states that "...variants meets the requirements of 35 U.S.C.§112, first paragraph as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins is routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence". Based on these guidelines, Applicants submit that the instant specification evidences the actual reduction to practice of a full-length native human PRO1185 polypeptide of SEQ ID NO: 399, with or without its signal sequence and of the nucleic acid of SEQ ID NO: 398. In addition, the specification provides detailed description about the cloning of variants and describes the gene amplification assay for testing nucleic acids in a PCR based assay. Thus, Applicants submit that the genus of nucleic acids that code for the nucleic acid of SEQ ID NO: 398 or variants and further, which possess the functional property that it is "amplified in a lung tumors" would encompass a genus that meets the requirements of 35 U.S. C. §112, first paragraph as providing adequate written description.

Further, the present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. Thus, one of skill in the art would know that Applicants had possession of the invention, as described in the instantly amended claims, and therefore request that this rejection be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 119-125, 127-128 and 132-138 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. Further, Claims 132-134 were rejected under 35 U.S.C. §112, second paragraph for being indefinite for reciting hybridization language without clear hybridization conditions.

Without acquiescing to the propriety of this rejection, Applicants have canceled references to "the extracellular domain" and "the extracellular domain....lacking its associated signal sequence" in the pending claims and have canceled claims 132-134 without prejudice or disclaimer to pursue the claimed subject matter in further continuation or divisional applications. Therefore, Applicants request that this rejection be withdrawn.

Priority

Applicants rely on the gene amplification assay for patentable utility which was first disclosed in U.S. Provisional Application 60/141,037, filed June 23, 1999, priority to which has been claimed in this application. Hence, Applicants should be entitled to at least an effective filing date of **June 23, 1999.**

Claim Rejections - 35 USC § 102

Claims 119-123 and 132-138 are rejected under 35 U.S.C. §102(b) as being anticipated by Hillier et al. (EST Acc. No. AA464988; deposited 8/5/1997).

Firstly, in view of cancellation of claims 132-134, this rejection is moot with respect to claims 132-134 and should be withdrawn. Further, Applicants submit that EST Acc. No. AA464988 teaches a sequence that has 53% overall similarity to SEQ ID NO: 398 and to the nucleic acid sequence encoding the polypeptide of SEQ ID NO: 399. The instant claims recite nucleic acid sequences that have 80-99% sequence homology to the nucleic acid of SEQ ID NO: 398 that are "amplified in lung tumors". Hillier does not anticipate such sequences. Thus, this rejection should be withdrawn.

Claims 119-122 and 132-134 are rejected under 35 U.S.C. §102(e) as being anticipated by Bandman et al. (USPN 6,183,968; EST Acc. No. AA464988; deposited 8/5/1997).

Applicants submit that EST Acc. No. AA464988 teaches a sequence that has 53% overall similarity to SEQ ID NO: 398 and to the nucleic acid sequence encoding the polypeptide of SEQ ID NO: 399. The instant claims recite nucleic acid sequences that have 80-99% sequence homology to the nucleic acid of SEQ ID NO: 398 that are "amplified in lung tumors". Thus, Bandman does not anticipate such sequences and this rejection should be withdrawn.

Claim Rejections - 35 USC § 103

Claims 119-123 and 135-138 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hillier (locus AA464988) in view of Gerald et al. (U.S.P.N. 5,989,834).

Further, Claims 119-122 and 132-138 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bandman et al. in view of Gerald et al. (U.S.P.N. 5,989,834).

As discussed above, the currently amended claims are not anticipated by Hillier nor Bandman for the reasons cited above,and hence, the primary references, Hillier and Bandman, are not prior art references under 35 U.S.C. §102 or 103(a). Since Gerald does not teach all the limitations of the currently pending claims, these rejections fall. Accordingly, these rejections should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C68).

Respectfully submitted,

Date: December 7, 2004

Daphne Reddy

Daphne Reddy
Reg. No. 53,507

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638
2074023